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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	11

DATE MAILED: 10/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,991	UITTERLINDEN ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8-19 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18 and 22* is/are allowed.

6)☒ Claim(s) *1-4, 6, 8-17,19, 21 and 23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to Paper No. 10, filed August 21, 2002. Applicants arguments presented in the response of Paper No. 10 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is non-final.

It is noted that page 18 of the specification is missing. Examiner kindly requests that applicant provide a replacement page 18 from the specification to complete their file as the copy of the present specification is incomplete.

The proposed drawing correction and/or the proposed substitute sheets of drawings, filed on August 21, 2002 have been Approved.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4, 6, 8-17, 19, 21, 23, and 25-30 are still rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for methods and kits for diagnosing susceptibility to bone fracture comprising detecting the presence of the G to T polymorphism at the Sp1 site of the collagen Iα1 gene, in conjunction with detecting the baT haplotype of the vitamin D receptor gene, the specification does not provide enablement for methods and kits for determining the susceptibility to bone fracture comprising detecting any allele of the collagen

Iα1 gene in conjunction with detecting the baT haplotype of the vitamin D receptor gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 3, 6, 8, 9, 10, 19, 21, 23, 25, 26 and 29 are broadly drawn to methods and kits for diagnosing susceptibility to bone fracture comprising analyzing the genetic material of a subject to determine which allele of the collagen Iα1 gene is present. The specification teaches susceptibility to bone fracture comprising the detection of the presence of the G to T polymorphism at the Sp1 site of the collagen Iα1 gene. The claims do not specify which allele, of the collagen Iα1 gene, in what copy number, is present in a subject to determine their susceptibility to bone fracture. Furthermore, the specification provides no guidance as to how to predictably identify additional alleles of the collagen Iα1 gene that are associated with bone damage. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which

the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate what allele in the collagen Iα1 gene may exist to cause a subject to be susceptible to bone fracture. The claims are drawn to a potentially very large genus of polymorphisms(i.e., any polymorphism or mutation in the collagen Iα1 gene), yet the specification teaches only one polymorphism in the collagen Iα1 gene associated with bone fracture(i.e., the G to T polymorphism at the Sp1 site). Therefore, the specification has not taught a representative number of species within the claimed genus. Furthermore, the specification does not provide sufficient guidance as to how to select additional alleles of the collagen Iα1 gene associated with bone fracture because the specification does not teach, for example, how modifying the collagen Iα1 gene product results in bone fracture nor does it teach where mutations may occur in the collagen Iα1 gene product which would cause a change in the gene product's activity and would make an individual more susceptible to bone damage. Therefore additional alleles can only be identified by randomly analyzing the collagen Iα1 gene sequence and determining whether any of these alleles are correlated with bone fracture. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

Furthermore, Claims 1-4, 6, 8-17, and 27-30 are also rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for methods for determining

susceptibility to bone fracture wherein the presence of the baT haplotype is detected, the specification does not provide enablement for methods for determining susceptibility to bone fracture wherein the presence of at least one of the b, a and T alleles is indicative of an increased susceptibility to bone fracture. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-4, 6, 8-17, and 27-30 are broadly drawn to a method of determining susceptibility to bone fracture wherein the presence of a haplotype comprising at least one of the b, a and T alleles is indicative of an increased susceptibility to bone fracture. The specification teaches the determination of susceptibility to bone fracture wherein the whole "baT" haplotype is indicative of an increased susceptibility. In fact, on page 4, line 17 of the specification applicant discloses that while having the "b" with "aT" haplotype is associated with increased risk of bone damage, a subject having the "b" with "At" haplotype is at a lower risk of fracture. The specification teaches that the power of predictability lies in the presence of all three alleles(baT) together, not in each allele separately. Furthermore, the specification teaches the finding that, "risk of bone damage is independent of bone density."(Pg. 5, line 23) Much unpredictability exists in this notion of the specification teaching that both the "baT" haplotype, and each allele individually(ie. b, a, and T) result in the same phenotype. Specifically, that the "baT" and "b", and/or "a" and /or "T" are all independent of bone density. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the

predictability in the art. The art teaches that much unpredictability exists concerning the presence of each allele singly. Especially concerning the relationship, or lack thereof, between each allele and bone density. Morrison et al.(Nature, 1994) teach that the presence of the same "b" allele in the vitamin D receptor gene, confers an increased bone density and therefore a contrasting, decreased risk of bone damage. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate which effect; an increased risk of bone damage or a deceased risk of bone damage will occur in response to the presence of "at least one of the b, a, and T alleles." The claims are drawn to a potentially very large genus of allelic compositions (ie b, ba, baT, a, aT, BaT, Bat, etc.), yet the specification teaches only one haplotype specifically that is associated with an increased risk of bone fracture, the "baT." Furthermore, the specification teaches only that the "bAt" and the "Bat" have lower risks of bone fracture than the "baT" but omits any teachings of how other allelic combinations would impact bone fracture(Pg. 4, lines 15-17). Therefore, additional predisposing haplotypes can only be identified by randomly analyzing each permutation of allele combinations and determining whether any of these permutations are correlated with bone fracture. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack

of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

Response to Arguments

In the response of Paper No. 10, Applicants traverse this rejection by stating that the specification is enabling for determining susceptibility to bone fracture by determining the claimed genus of polymorphisms or mutations in the collagen Ialpha1 gene because the specification has identified general methods for identifying the presence of polymorphisms in genes as well as methods that are well known in the art at the time of the invention. However, based on the lack of teachings in the specification, lack of predictability, and lack of working examples, undue experimentation is required to find all alleles whose detection is encompassed in the claims since the detection of no other allele is taught in the specification nor the art and such exploration would result in a research project.

With respect to claim 3, examiner points out that the scope of enablement rejection still stands since the claim still reads on a method of determining the presence of any allele of the collagen I alpha 1 gene, not just the T/G polymorphism at the Sp1 binding site in the first intron.

With respect to applicant's arguments concerning claim 6, examiner acknowledges that claim 6 is limited to a method for determining the copy number of the "S/s" allele of the collagen I alpha 1 gene, but applicant is still required to state which of the two, "S" or "s", is detected as indicative of increased susceptibility to bone fracture.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Morrison et al. (U.S. Patent No. 5593833) in view of Ahern(The Scientist, 1995).

Morrison et al. teach a method for determining the susceptibility to osteoporosis, whose "most serious endpoint is bone fracture"(specification page 1, lines 16-17), in a subject comprising the use of one or more nucleic acid primer molecules for amplification of a portion of the Vitamin D receptor gene(Col. 3, lines 25-27), means for determining whether the baT haplotype of said gene is present with primers specific for amplifying the *TaqI, BsmI* and/or *ApaI* polymorphisms (Col. 3 lines 28-35) and a means for indicating correlation between the presence of said haplotype and risk of osteoporosis(Col. 20, lines 57-65).

Morrison et al. do not teach a kit comprising the above components.

However, Ahern et al. teach that "more researchers are buying premade reagents and kits because they are convenient and they save time."(Pg. 4) The reference teaches that pre-existing reagents are more easily used when combined in a kit composition.

Therefore, it would have been obvious to one skilled in the art at the time the invention was made to have combined the primers and methods of Morrison in view of Ahern, for the expected benefit of generating a kit that provided a more convenient and time-saving means of detecting the baT haplotype of the VDR gene.

4. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morrison et al. in view of Ralston and in further view of Ahern(The Scientist, 1995).

Morrison et al. teach a method for determining the susceptibility to osteoporosis, whose "most serious endpoint is bone fracture"(specification page 1, lines 16-17), in a subject comprising one or more nucleic acid primer molecules for amplification of a portion of the Vitamin D receptor gene(Col. 3, lines 25-27), means for determining whether the baT haplotype of said gene is present with primers specific for amplifying the *TaqI, BsmI* and/or *ApaI* polymorphisms (Col. 3 lines 28-35) and a means for indicating correlation between the presence of said haplotype and risk of osteoporosis(Col. 20, lines 57-65).

Morrison et al. do not teach a method comprising one or more nucleic acid primer molecules for amplification of a portion of the collagen I alpha 1 gene, means for determining which allele of the collagen I alpha1 gene is present nor a kit comprising both the VDR gene, said collagen Ialpha1 gene reagents and a positive control.

However, Ralston teaches that the G to T polymorphism in the collagen Iα1 gene is associated with risk of osteoporosis(abstract). In view of Morrison's teachings of how to generate primers for the detection of a polymorphism, it would have been further obvious to one of ordinary skill in the art to have modified the method of Morrison so as to have included primers for detecting amplification of the collagen I alpha 1 gene for the expected advantage of generating a method that allowed for the analysis of both the baT haplotype of the VDR gene and the Sp1 polymorphism of the collagen Iα1 gene for individuals in the art wishing to determine an individual's susceptibility to osteoporosis.

Although, Morrison in view of Ralston does not teach combining all of the aforementioned reagents(for both genes) into a kit, Ahern teaches that "more researchers are buying premade reagents and kits because they are convenient and they save time."(Pg. 4) The reference teaches that pre-existing reagents are more easily used when combined in a kit composition.

Therefore, it would have been obvious to one skilled in the art at the time the invention was made to have combined the primers and methods of Morrison in view Ralston, and in further view of Ahern, for the expected benefit of generating a kit that provided a more convenient and time-saving means of detecting the baT haplotype of the VDR gene in addition to detecting the Sp1 polymorphism of the collagen Iα1 gene for increasing the sensitivity for determining susceptibility to osteoporosis.

Furthermore, with respect to claim 26, the combined references do not teach including a DNA control in the kit. However, it was conventional in the art at the time the invention was made to include the use of a DNA control in amplification methods to ensure the accuracy of the

method. Therefore, it would have been obvious to one skilled in the art at the time the invention was made to have included a DNA control in the kit of Morrison in view of Ralston for the expected benefit of generating a kit that provided a more accurate means of detecting the baT haplotype of the VDR gene although no specifically stated.

Allowable Subject Matter

Claims 18 and 22 are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Uitterlinden et al., Journal of Bone and Mineral Research, 1996, teach that the presence of the bAT haplotype is associated with low BMD. It also teaches that, "low genetic resolution can obscure an association between the BMD level and the VDR genotypes in studies using individual restriction enzyme recognition site polymorphisms."(Page 1244)

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

10/15/02

Sally Sakelaris

CARLA J. MYERS
PRIMARY EXAMINER